Perspectives of Novel Imaging Techniques for Staging, Therapy Response Assessment, and Monitoring of Surveillance in Lung Cancer: Summary of the Dresden 2013 Post WCLC-IASLC State-of-the-Art Imaging Workshop

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Abstract: Modern imaging techniques that can provide functional information on tumor vascularization, metabolic activity, or cellularity have seen significant improvements over the past decade. However, most of these techniques are currently not broadly utilized neither in clinical trials nor in clinical routine, although there is a large agreement on the fact that conventional approaches for therapy response assessment such as Response Evaluation Criteria in Solid Tumors or World Health Organization criteria—that exclusively focus on the change in tumor size—are of less value for response assessment in modern thoracic oncology. The aim of this article comprises two parts: a short review of the most promising state-of-the-art imaging techniques that have the potential to play a larger role in thoracic oncology within the near future followed by a meeting report including recommendations of an interdisciplinary expert panel that discussed the potential of the different techniques during the Dresden 2013 Post World Congress of Lung Cancer (WCLC) - International Association for the Study of Lung Cancer (IASLC) meeting. It is intended to provide a comprehensive summary about ongoing trends and future perspectives on functional imaging in thoracic oncology.

Key Words: Lung cancer, Staging, Response assessment, Diffusion weighted imaging, Dynamic contrast-enhanced CT, PET–CT, Dual-energy CT, Volumetric measurements

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Lung cancer is still the leading cause of cancer-related death in both men and women in the western world, with 80 to 85% of cases being non–small-cell lung cancer (NSCLC).[1] The past decade has seen significant breakthroughs in the understanding of the molecular biology of lung cancer. Signaling pathways that are vital for tumor growth have been identified and can be effectively targeted by novel pharmacologic agents, resulting in significantly improved outcome of patients with lung cancer.[2] Parallel to the progress in lung cancer treatment, imaging techniques aiming at improving diagnosis, staging, response evaluation, and detection of recurrence have also considerably advanced in recent years.[3] However, standard morphologic computed tomography (CT) and magnetic resonance imaging (MRI) as well as 2-[^{18}F]-Fluoro-2-deoxy-glucose (^{18}F-FDG) positron emission tomography–CT (PET–CT) are still the

currently most frequently utilized imaging modalities in clinical practice and most clinical trials.[4,5] Novel functional imaging techniques such as dual-energy CT (DECT), dynamic contrast-enhanced CT (DCE-CT), diffusion-weighted MRI (DW-MRI), perfusion MRI, and PET–CT (with tracers that are more specific than 18F-FDG) have not yet been broadly implemented, neither in clinical practice nor in phase I–III clinical trials.

In this context, Nishino et al.[6] recently reviewed personalized tumor response assessment in the era of molecular treatment in oncology. The authors concluded that the concept of personalized medicine with regard to cancer treatment has been well applied in therapeutic decision-making and patient management in clinical oncology. However, it was observed that the developments in imaging techniques for tumor response assessment had not paralleled advances in cancer treatment, and had not sufficiently incorporated state-of-the-art functional information. Functional information on tumor response is highly required because there is growing evidence that the current objective criteria for treatment response assessment based on structure alone may not reliably indicate treatment failure and do not adequately represent disease biology. Molecular-targeted therapies, immunological agents as well as stereotactic radiotherapy induce effects that differ from those induced by classic cytotoxic treatment including intratumoral hemorrhage, changes in vascularity, and tumor cavitation and thus require new criteria and/or approaches as patients may be inappropriately treated. Conventional approaches for therapy response assessment such as RECIST or WHO criteria that exclusively focus on the change in tumor size are of less value for response assessment of targeted drugs.[7,8]

The motivation for the organization of this novel imaging advisory board was the perception of the authors about the 'translation gap' between radiologists and pneumologists, thoracic oncologists, preclinical researchers, radiation oncologists, and thoracic surgeons. This 'translation gap' regards novel therapy approaches and state-of-the-art imaging techniques, especially with respect to the application of functional imaging techniques in clinical trials. The first *Advisory Board* entitled '*Potential Integration of Novel Imaging Techniques in Staging, Therapy Response Monitoring and Surveillance in NSCLC'* was held on December 7, 2013, in Dresden, Germany, one day after the '*Post-WCLC 2013 Meeting*'. The *Advisory Board* was divided in two main sessions. In the first educational part, invited imaging experts summarized the current scientific evidence on novel functional imaging techniques and weighed the potential pros and cons for the integration of these techniques into future clinical trials. In the second discussion part, all invited multi-disciplinary experts discussed the value and the applicability of novel functional imaging techniques for various clinical scenarios.

Accordingly, this article comprises two parts: a short review of the relevant subject areas followed by a meeting report including recommendations of the expert panel. It is intended to provide a comprehensive summary about ongoing trends and future perspectives on functional imaging. The advisory board should be considered as a work in progress meeting that is intended to be continued in 2015.

Educational Part: Imaging Techniques

Volumetric approaches for therapy monitoring

The expert committee discussed volumetric data analysis and there was a broad consensus about the need for volumetric tumor measurements based on the available literature. The 7th edition of the TNM-staging system demonstrated the significance of the primary tumor extent on the prognosis of patients with NSCLC.[1] Thus, three-dimensional methods to accurately assess the primary tumor extension before and during therapy have gained increased attention over the past years, because it has been demonstrated that even in CT studies with consistent scan parameters, minor variations in slice position or patient orientation considerably influence the results of tumor measurements.[9] Moreover, inter-assessor variability might affect tumor response assessment with potential therapeutic consequences.[9] Therefore, advanced methods for precise and reproducible tumor measurements over time are clinically needed.[10]

Several studies have demonstrated that tumor volume measurements in NSCLC have a significantly higher reproducibility than measurements of maximum tumor diameters.[11–15] The importance of tumor volume measurements for the prediction of treatment outcome after chemotherapy and radiotherapy has also been evaluated. All of these studies reported the superiority of volumetric measurements over RECIST criteria.[16–18] These findings are even more important in patients undergoing targeted therapies. Here, the limited ability of RECIST criteria to characterize tumor response and, therefore, to guide therapeutic decisions are more pronounced due to the differences in response patterns, such as decreasing tumor density, cavitation, and intra-tumor hemorrhage.[4,6,19–22] A recent study on patients with advanced NSCLC and epidermal growth factor receptor (EGFR) mutations showed that only the tumor volume decrease at 8 weeks of EGFR-tyrosine kinase inhibitor (TKI) therapy was associated with longer survival.[23] Based on the results of these and other studies, tumor volume measurements using semi-automated software tools could be easily and cost effectively implemented in the design of future clinical trials, helping to overcome RECIST limitations related to targeted therapies.

Novel morphologic approaches for the assessment of therapy response

As mentioned above, tumor response assessment in patients undergoing targeted therapies requires new strategies beyond RECIST and WHO criteria. Thus, Lee et al.[24] evaluated new response criteria in patients treated with EGFR-TKIs compared with RECIST and proposed new criteria for a more accurate response assessment in patients with NSCLC undergoing TKI therapy. In this study, a decrease of tumor attenuation in Hounsfield units was an accurate marker of therapy response even in tumor s with a less than 30% decrease in maximum size. The decrease in tumor attenuation was caused by the high incidence of tumor cavitation after EGFR-TKI therapy as a surrogate of central tumor necrosis. This sign of therapy response was not observed in patients undergoing standard chemotherapy. By applying these criteria, patients classified as responders showed a higher median overall survival (18.4 months) than

patients with poor response (8.5 months). In contrast, RECIST criteria were negative in 16 patients that achieved response according to the new criteria. In addition, tumor cavitation was used as a biomarker of therapy response in a recent phase II trial of neoadjuvant bevacizumab plus chemotherapy.[25]

Dual-energy CT

DECT, a relatively new CT technique, allows absolute quantification of iodinated contrast material in tumor tissues. The physical principle of DECT is based on the differential attenuation of iodinated contrast material depending on the tube voltage (Fig. 1).[26,27] By applying two different X-ray spectra during a routine contrast-enhanced chest CT examination, the total amount of iodinated contrast material as a surrogate marker of blood volume within a tumor can be calculated without an additional CT examination. The main advantage of DECT is its easy application that causes no additional procedural costs and does not require increased radiation doses or additional injections of iodinated contrast materials (Fig. 2). The DECT technique is provided by all major CT manufacturers and generates standard CT images that allow all conventional morphological measurements, with the inherent advantage that the tumor blood volume can also be measured. Furthermore, DECT datasets can be used to calculate noncontrast CT images from contrast enhanced CT data without the need of a separate unenhanced scan. Using these virtual noncontrast datasets, calcifications can be visualized and potentially differentiated from intra-tumor contrast enhancement.[28] Even more important, DECT could potentially help to differentiate between intra-tumor hemorrhage and contrast enhancement as for example shown in gastrointestinal stromal tumors under TKI therapy.[29] This information provided by DECT may gain more importance within the future because changes in tumor density caused by intra-tumor hemorrhage are more frequently observed during targeted therapy than during cytotoxic chemotherapy.[30] Several studies have applied DECT for the differentiation between benign and malignant lesions, to improve tumor visualization, and to assess treatment response in renal cancer, hepatic cancer, and gastrointestinal stromal tumors .[29,31,32] One study evaluated the usefulness of DECT for the characterization of pulmonary nodules.[28] In this study, DECT-measured iodinated contrast enhancement correctly classified 45 of 49 nodules into benign versus malignant tumors. Besides the classification of pulmonary nodules, DECT could potentially be applied to evaluate the therapy response by analyzing changes in the tumor iodine and, accordingly, blood volume, especially in patients undergoing anti-angiogenic-targeted therapies.

One study showed a strong correlation between the maximum standardized uptake value (SUV_{max}) of ^{18}F-FDG PET–CT and the tumor iodine content as calculated from DECT datasets.[33] Another study by Kim et al.[34] evaluated the applicability of DECT for response assessment in NSCLC patients treated with anti-angiogenic agents and found discordant responses between RECIST- and DECT-based response assessment. The authors concluded that DECT is a useful tool for response evaluation after anti-angiogenic treatment by providing quantitative data on tumor enhancement and vascularity without obtaining noncontrast-enhanced images.[34] Ogawa et al.[35] proposed DECT iodine measurements for advanced assessment of mediastinal lymph node vascularity in patients with lung cancer. The fact that DECT can be used for the analysis of pulmonary perfusion represents another advantage. Chae et al.[28] compared DECT perfusion imaging and lung perfusion scintigraphy for the prediction of postoperative lung function in patients undergoing lung resection. In this study, postoperative lung function was more accurately predicted by DECT than by perfusion scintigraphy. Beside the visualization and quantification of iodinated contrast material, the spectral DECT effect can also quantify inhaled xenon to assess pulmonary ventilation and therefore offers an alternative to pulmonary ventilation scintigraphy.[36]

In summary, DECT could be easily integrated into clinical trials, because the technique is widely available and requires only minor changes on most state of the art CT scanners. DECT provides additional information on tumor blood volume as a surrogate for, for example, tumor response, as well as pulmonary perfusion and ventilation without the requirement of an increased radiation dose (Table 1).

Dynamic contrast-enhanced CT

Tumor angiogenesis leads to an increase of regional blood flow (BF) and blood volume (BV) and, thereby, contrast-enhancement of lung cancer tissue. Tumor perfusion

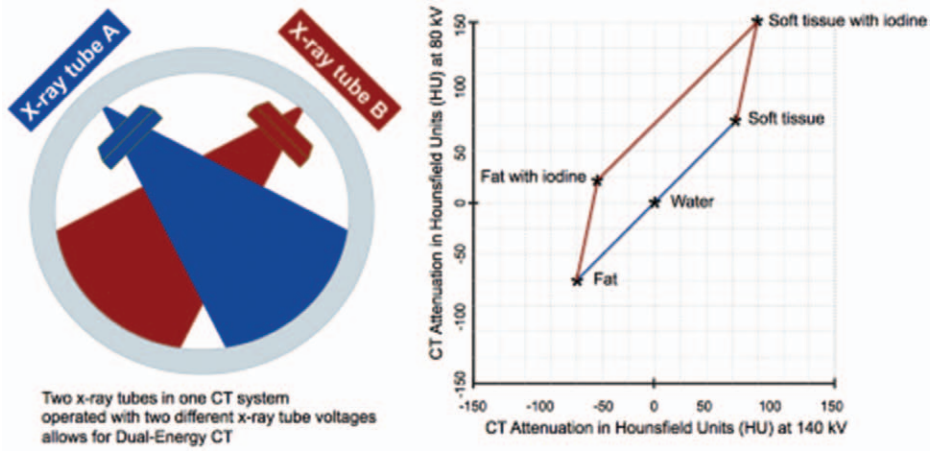

FIGURE 1. The figure demonstrates the principle of dual-energy CT. Dual-source CT systems are one way to acquire dual-energy CT datasets by operating the two X-ray tubes with two different tube voltages at the same time. Materials with high anatomic numbers like iodine show a different X-ray attenuation depending on the applied tube voltage (image on the *left*). The different tissue attenuation at different tube voltages allow to selectively visualize and quantify iodinated contrast material and thus blood within the tumor. CT, computed tomography.

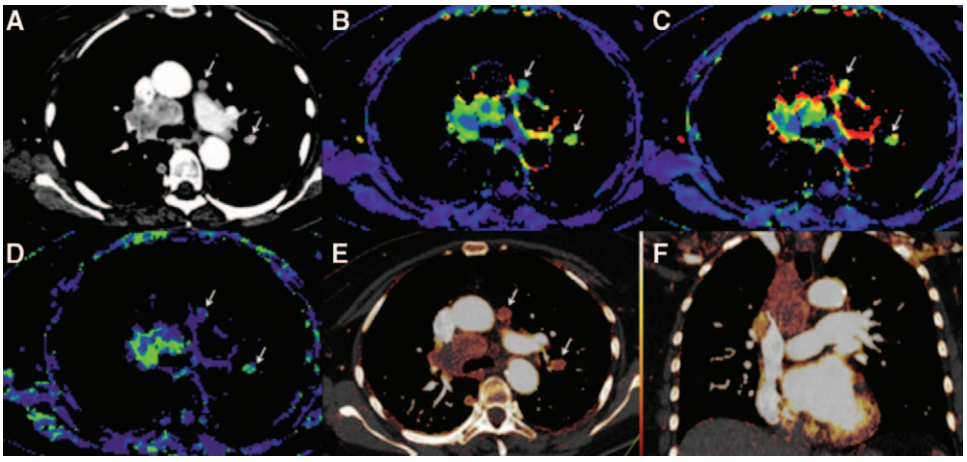

FIGURE 2. CT images of a 68-year-old patient with a central NSCLC that underwent whole tumor volume dynamic contrast-enhanced CT (*A–D*) as well as dual-energy CT for tumor staging before TKI therapy. *A*, One late arterial phase gray scale image 25 seconds after the contrast agent administration. *B–D*, Color-coded images representing blood volume (*B*), blood flow (*C*), and the mean transit time (*D*) of the contrast agent through the tumor. *E* and *F*, The corresponding dual-energy CT images. The blood volume (tissue iodine content) is color coded within the image and correlates with the blood volume from the dynamic series (*B*). The *arrows* demonstrate a highly perfused lymph node metastasis as well as a contralateral intrapulmonary metastasis. CT, computed tomography; NSCLC, non–small-cell lung cancer, TKI; tyrosine kinase inhibitor.

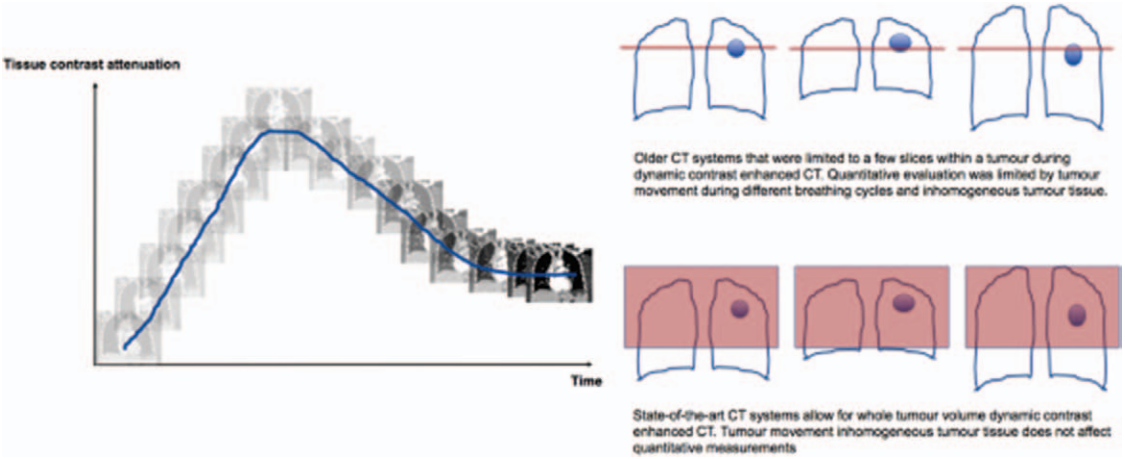

FIGURE 3. *Left figure* The basic principle of dynamic contrast-enhanced CT. Subsequently after the start of the intravenous administration of iodinated contrast material the anatomic region of interest is scanned several times with a very short so called inter-scan delay (usually 1.5–2.5 seconds in thoracic malignancies) between the different acquisitions. The measurement of the tissue contrast attenuation in all different acquisitions allows calculation of time intensity curves as well as calculation of multiple quantitative tissue parameters including blood volume, blood flow, tissue permeability, and the contrast agent mean transit time through the tissue. *Right figure* The advantage of whole tumor dynamic contrast-enhanced CT (*lower row*) that is not affected by tumor motion during different breathing cycles as well as inhomogeneous tumor tissue. *Upper row* Limitations of dynamic contrast-enhanced CT with older CT systems that limited the clinical value of the technique. CT, computed tomography.

and therapy-induced perfusion changes can be quantified by DCE-CT. DCE-CT can assess tumor density at different times, based on consecutive CT scans that are acquired after the injection of contrast material (Fig. 3). The technique provides quantitative data of tumor BF, BV, permeability, and the mean transit time of iodinated contrast material through the tumor (Fig. 2).[37–43]

The feasibility of DCE-CT to characterize pulmonary nodules has been proven in a prospective, multicenter trial evaluating DCE-CT for the classification of benign and malignant pulmonary nodules.[41] Moreover, several studies have correlated the results of DCE-CT to histological parameters of tumor angiogenesis such as micro-vessel density (MVD) and vascular endothelial growth factor (VEGF) expression. Tateishi et al.[44] for example analyzed the correlation of tumor enhancement over time with MVD and VEGF expression in 130 patients with histologically proven NSCLC. They found a significantly higher peak enhancement in VEGF-positive tumors than in VEGF-negative tumors. In addition, peak-enhancement of VEGF-positive tumors had

a significantly positive correlation with MVD (r = 0.65). Moreover, lymph node-positive lung cancer patients showed a higher peak enhancement, VEGF expression, and MVD than lymph node-negative patients.

DCE-CT may be used for the assessment of tumor response to targeted therapy or radiotherapy. It has been reported that micro-vascular damage is a key mechanism in tumor response to radiation.[45] Therefore, reduced volume of the vascular bed after radiation therapy is reflected by reduced BF, BV, and permeability. Ng et al.[46] demonstrated that hypo-fractionated radiotherapy increases both the tumor vascular blood volume and the permeability of NSCLC. Wang et al.[47] demonstrated that NSCLCs with higher perfusion values, as measured by DCE-CT, are more sensitive to radiochemotherapy than tumors with lower perfusion values. Moreover, the study suggests that after radiochemotherapy, DCE-CT results significantly predict early tumor response and overall survival among patients with NSCLC. In another study by Lind et al.,[48] tumor BF measured by DCE-CT in 23 patients with advanced NSCLC correlated with the response to anti-angiogenic and anti-EGFR-targeted therapy, e.g., sorafenib and erlotinib. DCE-CT was performed at baseline as well as 3 and 6 weeks after the initiation of treatment. Tumor perfusion was lower in responders than in nonresponders at week 3 and 6. Patients with a large decrease of BF at week 6 tended to have a longer progression-free survival. Fraioli et al.[49] performed DCE-CT at day 40 and 90 after initiation of conventional and anti-angiogenic chemotherapy in patients with advanced lung adenocarcinoma. In this study, BF, BV, and permeability values were higher in responding patients than in that of the other patients, with significant differences for BF, BV, and permeability at second follow-up. The time to peak contrast enhancement was higher in nonresponding patients than in that of treatment responders. Despite these promising results, DCE-CT has not yet been established as a standard procedure in clinical routine as the applicability of this technique was limited in the past because data acquisition was restricted to single or few slides throughout the tumor. However, with currently available state-of-the-art CT systems, whole tumor coverage with an acceptable radiation dose using low tube voltage settings became feasible.[37,46] This scanner equipment has recently been demonstrated to achieve a substantial intra-observer agreement for lung cancer DCE-CT measurements, encouraging its use for tumor characterization and therapy response monitoring.[50] Moreover, whole tumor DCE-CT may allow advanced subclassification of different lung cancer entities.[51] Thus, DCE-CT seems to be an attractive and cost–effective method to monitor response to treatment in patients undergoing anti-angiogenic therapies although one has to acknowledge that based on the currently available evidence the technique is still not "*ready for prime time*" to replace RECIST of WHO criteria in prospective clinical trials (Table 1).

Positron emission tomography

^{18}F-FDG PET–CT is the current clinical gold standard imaging modality for the primary staging of NSCLC and small-cell lung cancer and has been recommended by recent guidelines.[52–54]

In addition to primary tumor staging,^{18}F-FDG PET–CT has been shown to be superior to standard CT and MRI for the detection of recurrent disease after surgery, local ablative therapies such as microwave ablation and chemotherapy.[55–64] According to the **P**ositron **E**mission Tomography **R**esponse **C**riteria in **S**olid **Tumor**s (PERCIST) guidelines, a reduction in ^{18}F-FDG PET uptake of 30% is defined as a metabolic response, whereas an increase of 30% is defined as progression.[65] Moreover,^{18}F-FDG PET–CT defines more precisely the target volumes for both, conventional as well as stereotactic radiotherapy planning.[66–68]

The pyrimidine analog 3′-deoxy-3′-[^{18}F]-fluorothymidine (^{18}F-FLT) is phosphorylated by thymidine kinase 1 into 18F-FLT monophosphate after cellular uptake, leading to intracellular sequestration of radioactivity.[69] Because thymidine kinase 1 is a principal enzyme in the salvage pathway of DNA synthesis, 18F-FLT PET reflects cellular proliferation. According to several studies, ^{18}F-FLT PET can be used to monitor the response to TKI therapies in patients with NSCLC.[69] A phase II trial by Zander et al.[70] demonstrated that an early ^{18}F-FLT PET response 1 week after the initiation of treatment predicted significantly longer PFS. Moreover, Kahraman et al.[71] showed that metabolically active volume measurement in early ^{18}F-FLT PET may have an additional predictive value for the response of patients with advanced NSCLC treated with erlotinib. Based on the currently available literature, 18F-FLT PET is a promising measure for assessing the response to targeted therapy in patients who have a higher likelihood of EGFR mutations in their tumors. Thus, the role of ^{18}F-FLT PET will likely gain more importance in nonsmoking Asian patients with adenocarcinoma as well as other patient cohorts that are more prone to EGFR mutations.[72]

[^{68}Ga]-DOTA-Tyr^{3}-octreotate (^{68}Ga-DOTA-TATE) PET has shown superiority when compared with ^{18}F-FDG PET for the staging and response evaluation of pulmonary neuroendocrine tumors (Table 1).[73]

Magnetic resonance imaging

Multi-parametric MRI is already well established and recommended as the gold standard imaging modality for the assessment of brain metastasis.[74] Moreover, MRI has the best diagnostic capabilities to visualize the mediastinal and chest wall infiltration due to both its inherent high soft tissue contrast and its ability to acquire dynamic cine-MRI sequences that allow to visualize tumor movement during several heart beats or breathing cycles. Another indication for MRI that is already widely employed is the assessment of bone metastasis. Several studies as well as meta-analysis have demonstrated that MRI is of equal or only slightly less diagnostic accuracy when compared with both 18F-FDG PET–CT and bone scintigraphy.[75–77]

Beyond those indications, experimental studies in recent years have mainly focused on DW-MRI as a tool for accurate staging of mediastinal lymph nodes and the evaluation of tumor response during therapy. DW-MRI visualizes the microscopic movement of water molecules within tissues and has been proposed for the differentiation between benign and malignant lymph nodes. In metastatic lymph nodes, diffusion is limited due to the obstruction of lymph nodes by tumor cells (Fig. 4). Therefore, metastatic lymph nodes have significantly

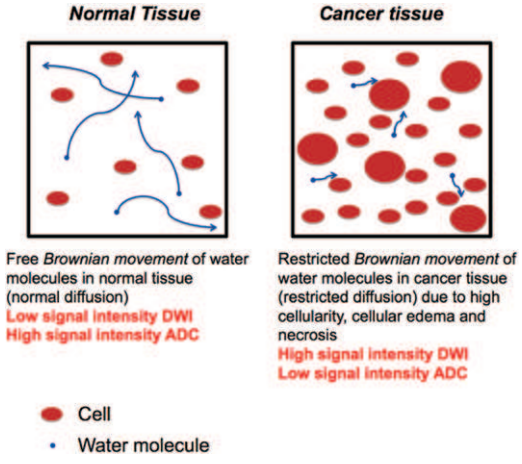

FIGURE 4. The figure demonstrates the principle of DWI with magnetic resonance imaging. Water molecules show a random Brownian movement in normal tissue leading to low signal intensity on DWI images. In cancer tissue with more cellularity and/or cellular edema, the Brownian movement is restricted which can be visualized on DWI images and quantified using the ADC. DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.

lower apparent diffusion coefficient (ADC) values than that of the benign lymph nodes.[78]

Although the role of MRI, especially DW-MRI, for lymph node staging of NSCLC has not been as well studied as that of ^{18}F-FDG PET–CT, recent studies indicate that MRI and 18F-FDG PET–CT may provide comparable diagnostic information.[79–83] In a study by Wu et al.,[79] DW-MRI provided even more specificity in preoperative mediastinal lymph node staging when compared with ^{18}F-FDG PET–CT, with no significant difference in sensitivity. Hasegawa et al.[84] used DW-MRI in 42 patients with NSCLC before surgical resection. In this study, DW-MRI detected 80% of all histopathologically proven metastases and accurately identified 97% of patients without mediastinal lymph node metastasis. Nomori et al.[85] directly compared the accuracy of DWI-MRI and 18F-FDG PET–CT for determining N category in patients with NSCLC and compared the results of both modalities to those of histopathological examination. Among 734 analyzed lymph node stations, histopathology revealed 36 metastatic and 698 nonmetastatic lymph nodes. There was no significant difference between DW-MRI and 18F-FDG PET–CT in the detection of metastatic lymph node stations. However, DW-MRI was more accurate than 18F-FDG PET–CT in the identification of nonmetastatic lymph node stations because of the lower rate of false-positive results.

A study by Ohno et al.[86] compared the predictive values of DWI-MRI and 18F-FDG PET–CT for tumor response to therapy and survival in patients with NSCLC undergoing combined chemoradiation therapy. A total of 64 patients with stage III NSCLC underwent pretherapeutic DW-MRI and 18F-FDG PET–CT. For the quantitative prediction, the ADC values for DW-MRI and the SUV_{max} for PET/CT were measured and compared. In this study, DW-MRI showed significantly better specificity and accuracy for the prediction of response and survival when compared with ^{18}F-FDG PET–CT.[86]

^{23}Na MRI is a very new imaging technique that allows the visualization of tissue 23Na concentrations. It might therefore represent a valuable functional biomarker for tissue viability during and after therapy. Proliferating malignant cells have an abnormally high ^{23}Na content, because the normal intracellular ^{23}Na concentration of approximately 10 to 15 mmol/liter is elevated as a result of altered Na^+/H^+ transport kinetics and pH.[87] Moreover, angiogenesis and increased interstitial space also lead to increased 23Na tissue concentration in tumors. Although ^{23}Na-MRI has been described more than 20 years ago, it was technically limited to experimental animal studies or neurological applications in humans.[88] However, technical developments in MRI and the commercial availability of ^{23}Na-tuned coil systems have now extended the clinical application.[89–94] So far, only one study has evaluated the feasibility of ^{23}Na-MRI in patients with NSCLC. It concluded that ^{23}Na-MRI could provide valuable clinical information about tumor viability.[95] However, the technique has not been systematically evaluated in clinical studies with respect to staging accuracy, response assessment, and prediction of patient outcome (Table 1).

PET–MRI

PET–MRI has been introduced and employed in a few institutions over the past 5 years worldwide. The potential advantage of PET-MRI is best described by the combination of metabolic/functional PET information, high soft tissue contrast of MRI, and functional information provided by DW-MRI. However, MRI has some inherent limitations in lung imaging. One limitation is the low proton density, which is responsible for the low signal-to-noise ratio of lung parenchyma. Another limitation results from the multiple air–tissue interfaces with large magnetic field gradients, causing susceptibility artifacts and inter-voxel phase dispersion of spins that lead to a very low T2* relaxation time of the lung parenchyma. The currently available literature is insufficient to establish a clear role for the clinical role of PET–MRI for lung cancer imaging. One study systematically compared 18F-FDG PET–CT and 18F-FDG PET–MRI in 22 patients with confirmed NSCLC for primary and locoregional lymph node staging using histopathology as reference standard.[96] In this study, 18F-FDG PET–CT compared equal to ^{18}F-FDG PET–MRI. Thus, the authors concluded that 18F-FDG PET–MRI does not provide advantages in thoracic staging of NSCLC patients.[96] Another study that compared 18F-FDG PET–CT and 18F-FDG PET–MRI in 227 patients with different tumors including NSCLC, head and neck and colon carcinoma did not find statistically significant superiority of ^{18}F-FDG PET–MRI to ^{18}F-FDG PET–CT.[97]

In summary, no studies have clearly described superiority of ^{18}F-FDG PET–MRI over 18F-FDG PET–CT for lung cancer staging and assessment of treatment response. However, future studies are required to investigate whether a combination of metabolic PET information and DW-MRI-measured ADC values could improve diagnostic accuracy of mediastinal lymph node staging. Such combination has been described as successful by one study that did not use a hybrid PET–MRI system (Table 1).[98]

TABLE 1. Strengths, Potential Indications and Limitations of the Discussed Imaging Techniques *at a Glance*

Imaging Technique	Strengths and Indications	Limitations
Dynamic contrast-enhanced CT	• Absolute quantification of tumor perfusion parameters possible: ◦ Blood flow ◦ Blood volume ◦ Mean transit time ◦ Tumor permeability • Relative in inexpensive imaging technique as it can be included into a regular staging CT and only requires approximately 15 minutes more scanner room time • Robust imaging technique that generates comparable results between different scanners from different vendors if protocols are adapted • Reproducible for follow-up examinations. • Potential best indications: ◦ Patients undergoing anti-angiogenic therapy • High spatial resolution	• Requires state of-the-art CT systems that allow whole umor coverage to compensate for: ◦ Tumor motion between the different acquisitions ◦ Inhomogeneous tumor tissue if only a small part of the tumor is covered as it was with previous CT system generations the reproducibility to image identical areas of a tumor during follow-up examinations is almost impossible • Additional radiation dose to the patient requires appropriate indication after the risk has been weigh up against the benefit of the additional information provided by the additional examination • Additional amount of contrast material (usually between 40 and 60 cc) • Requires special training for radiologists and technicians
Dual-energy CT	• Imaging of tumor vascularization • Provides standard CT images that allow all standard measurements (e.g., RECIST, WHO, mWHO etc.) while at the same time quantitative information about the tumor blood volume can be calculated • No additional radiation dose, contrast material and CT room time → Potential technique for *all* patients • Easy implementation in clinical routine with no additional costs • Assessment of tumor blood volume during therapy • Correlates with ^{18}F-FDG tumor uptake Potential better differentiation between tumor and atelectasis	• Requires state of-the-art CT systems that provide dual-energy CT • Low current evidence level requires more implementation into clinical trials
Diffusion-weighted MRI	• Imaging of tumor cellularity • Good correlation with ^{18}F-FDG PET–CT for mediastinal lymph node assessment with studies indicating potential higher specificity • High accuracy for bone metastasis similar to scintigraphy and ^{18}F-FDG PET–CT • Easy integration into standard MRI examination protocols without relevant additional costs (slightly longer examination time) • Provides functional and quantitative information about tumor cellularity • High potential for patients undergoing *targeted therapies* especially TKI therapies because the technique quantifies tissue cellularity	• No standardization between different vendors • Values are influenced by differences in MRI scanner field strengths and the applied sequences. Need for standardized DWI-MRI examination protocols • Not applicable for patients with MRI contraindications (Pacemaker etc.). • Vulnerable to image artifacts • Low current evidence level for the value of therapy monitoring
Sodium (^{23}Na) MRI	• Visualization and quantification of tissue sodium concentration • Malignant tumors show higher tissue sodium concentrations • High potential for very early response assessment in patients undergoing targeted therapies since changes in the Na+/K+ATP-ase pump and thus the tissue sodium concentration appear before definite cell death	• Research technique with poor evidence in lung cancer imaging • Long examination times • Poor spatial resolution • No broad availability • Not applicable for patients with MRI contraindications (Pacemaker etc.)
3′-deoxy-3′-[^{18}F]-fluorothymidine PET	• Specific marker for cellular proliferation • Biomarker for early response assessment • Already good evidence provided by high quality clinical studies • Potential best indication in patients undergoing TKI therapies in which early response assessment is important	• Expensive additional procedure with limited availability • No standardized protocols and standardized uptake value reference values

CT, computed tomography; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization; mWHO, modified World Health Organization criteria; FDG, fluoro-2-deoxy-glucose; PET, positron emission tomography; TKI, tyrosine kinase inhibitor; MRI, magnetic resonance imaging.

SUMMARY OF DISCUSSION: RECOMMENDATIONS

GENERAL COMMENTS

After the summary of novel imaging techniques, it became clear that there is a need for interdisciplinary interaction on imaging, as there is a lack of knowledge among radiologists about clinically useful measures and required radiology research, as well as among clinicians about ongoing developments and opportunities in imaging. All participants agreed that the communication between radiologists and clinicians needs further improvement in quantity and quality. Moreover, the communication between radiologists and clinicians on ongoing developments and their potential applications in clinical trials should be formalized and accelerated. There was also a general consensus about the need for more and earlier integration of lung cancer radiology specialists into the planning of clinical trials. This should ensure that the most

appropriate imaging methods are applied and further validated in future clinical trials investigating targeted therapies.

Overall, it was considered essential that in the era of molecular oncology the radiology community should get more actively involved in clinical trials and patient care.

Dual-Energy CT

Although DECT is now broadly available and comes with no additional cost or increased radiation doses, the knowledge and awareness about this technology among lung cancer specialists is still limited. In the educational part of this article, available data and potential applications are described. Points of discussion included the characterization of pulmonary nodules, which might be an important application for DECT in the context of lung cancer screening algorithms that would potentially reduce the number of follow-up examinations in patients with positive findings. However, it has to be considered that CT examinations for lung cancer screening are generally performed with low dose noncontrast-enhanced CT. Thus, DECT could only help to further characterize nodules that have been detected in those low dose noncontrast-enhanced CT examinations. The correlation between DECT and PET glucose uptake in a single center trial is encouraging and warrants further investigation. It was stated that DECT might be helpful for early response evaluation in targeted therapies, because standard RECIST criteria are obviously insufficient in this setting.

Recommendations

It was agreed in the discussion that whenever possible DECT should be implemented as a standard method in clinical trials to provide more evidence for its role in the future, particularly as advanced response parameter. In screening programs, DECT could be a valuable tool to better differentiate between benign and malignant lesions. It is recommended that data of large patient numbers should be collected.

Thus, more centers should prospectively collect standardized DECT data to generate more evidence on this promising imaging modality. DECT data could also be potentially useful for inclusion into upcoming TNM editions.

Whole Body MRI

The advantages or differences of MRI compared with CT are well known. MRI should be seen as a complementary imaging tool for specific questions where the higher soft tissue resolution of MRI is relevant (mediastinal and chest wall infiltration is of clinical importance). However, it was acknowledged that the quality of MRI as well as the duration of the procedure has improved over the past years. Thus, the question is whether the fields of MRI application could be enlarged to an application in the staging algorithm of lung cancer patients. This would be particularly relevant for the unsolved problem of noninvasive mediastinal lymph node staging. Today, whole body MRI scans can be obtained within 40 minutes, but very little evidence exists about the role of whole body MRI in the context of lung cancer staging. It was discussed that brain, bone, and T4 tumors invading the mediastinum and chest walls are potential indications for MRI. However, the additive benefit to ^{18}F-FDG PET–CT needs further evaluation.

Recommendations

It was agreed that stage III lung cancer patients would be the most interesting target group to investigate the significance of whole body MRI. This group of patients represents almost one-third of newly diagnosed lung cancers but is very heterogeneous in terms of staging, treatment, and prognosis. Exact assessment of the local disease and exclusion of distant disease is crucial to guide treatment in these patients. It is recommended to determine to what extent whole body MRI, in comparison and in addition to ^{18}F-FDG PET–CT, will influence treatment decisions, especially in stage III lung cancer in which the high rate of brain metastasis especially requires MRI due to the superiority for the detection of brain metastasis compared with ^{18}F-FDG PET–CT. Likewise, the possible combination of MRI and PET in combined PET/MRI systems opens new opportunities and merits further investigation.

PET–MRI

Among the topics discussed were current limitations in terms of worldwide availability and, therefore, impact as well as existing reimbursement issues. Nonetheless, this method might be a powerful tool warranting further evaluation due to its great potential in differentiating soft tissues and due to the improvement of mediastinal lymph node staging by a PET and DW-MRI combination. This is of special interest in T4 tumors, where invasion of surrounding structures is very difficult to be sufficiently clarified. In particular, the reassessment of T4 tumors after neoadjuvant therapy to redefine operability in specialist units is an unmet need where PET–MRI might help. Likewise, staging of mediastinal lymph nodes needs to be improved, and PET–MRI could especially increase specificity.

Recommendations

As a first step, PET–MRI should be investigated in clinical trials on stage III lung cancer patients. PET–MRI should be used for the evaluation of the mediastinum and T4 tumors and should be compared with PET–CT with respect to a potentially improved mediastinal lymph node staging (either with dedicated hybrid PET–MRI systems or with fused image datasets).

New PET Tracers

In addition to ^{18}F-FDG PET–CT, which is now an integral part of the diagnostic algorithm in lung cancer, there are other promising radionuclides that have hardly been investigated in clinical trials so far. Unmet needs identified during the discussion were the diagnosis of neuroendocrine tumors, early response prediction for targeted therapies (e.g., EGFR-TKIs), and the evaluation of patients after stereotactic radiotherapy, because 18F-FDG PET is not sufficient to distinguish between inflammation and vital tumor tissue. However, the low number of GCP-conform radiopharmacies limits the development and evaluation of new tracers for the molecular characterization of tumors in vivo.

Recommendations

^{68}Ga-DOTA-TATE PET should be used as an additional imaging modality in neuroendocrine tumors. 18F-FLT is an example for a marker of cell proliferation that merits

further exploration as an early response predictor in patients undergoing targeted therapy. Leading centers should consider budgeting for on-site radiopharmacies to develop companion diagnostic tools for the guidance of targeted therapy. Response to neoadjuvant therapy should be used as a 'window of opportunity' for further research of functional tracer development to correlate tracer uptake with resected tumor tissue.

Specific Issues—Immunotherapy

Data are not sufficient to recommend any specific functional imaging modality for special use in patients that undergo immunotherapy and current technology lacks to differentiate accurately between pseudoprogression and progression. 18F-FDG PET may be limited by the problem of chronic inflammation induced by immunomodulatory therapy.

Recommendation

Data about initial experiences with different modalities should be collected to generate hypotheses to be subsequently tested in clinical trials. There was consensus that the theoretically most promising techniques within the context of response assessment in patients undergoing immunotherapy are DCE-CT and DECT. These 'markers' could detect changes in tumor vascularity, especially if pseudoprogression is suspected. 18F-FLT PET–CT is a marker of cell proliferation. There was a consensus that molecular imaging modalities have to be developed for targeted therapies.

Specific Issues–Follow-up after Ablative Therapies

Initially increased density of lung parenchyma, cavitation, and fibrotic changes are observed after thermoablation and stereotactic body radiation therapy (SBRT). There is no knowledge on how to follow up these patients. Preliminary data suggest DCE-CT and 18F-FDG PET–CT as useful imaging modalities for follow-up analyses of patients that have undergone SBRT or thermo-ablation. However, 18F-FDG PET–CT was not considered as useful within the first 12 months after thermo-ablation and SBRT due to a false-positive inflammatory/postprocedural tracer uptake.

Recommendations

There was broad consensus about the requirement of studies that systematically evaluate response assessment and observation of recurrence after thermoablation and SBRT. Functional imaging techniques should be integrated prospectively within clinical trials on patients undergoing SBRT and thermoablation. In this context, DECT, DCE-CT as well as DW-MRI are the most promising functional imaging techniques and should be prospectively studied.

Specific Issues–3D Reconstruction

As another important issue, the discussion identified the clinical need for a preoperative and standardized 3D reconstruction of thoracic vascular and trachea bronchiolar structures before video-assisted thoracoscopic surgery. However, it was pointed out that most centers do not provide standardized 3D reconstructions although the usefulness has been demonstrated in clinical studies.[99–101] Thus, standardized 3D multi-planar reformations would be of great value for surgeons to improve the planning of the procedure.

Recommendations

3D reconstruction can also be retrospectively done with any obtained CT image data derived from slices of 0.6 to 1.5 mm, without the need for CT raw data storage. Thus, the communication between surgeons and radiologists and the training of radiologists on the requirements and expectations of thoracic surgeons need to be enhanced. Regularly performed interdisciplinary workshops could help to overcome these obstacles.

Specific Issues–Standardized Radiological Reporting

The level of satisfaction with standard reports of local radiologists was intensively discussed. It was agreed that radiological reports should be more standardized and structured to include as much information as possible. The TNM stage should not be solely based on radiological imaging but on comprehensive clinical evaluations. Thus, radiology reports should include all descriptive and quantitative data obtainable from images that can help to generate the best possible clinical TNM staging. There was a general perception that many radiology reports do not describe suspected lymph nodes by using published, internationally agreed lymph node maps that would be additionally important for accurate TNM staging.[102] It is important to emphasize that the IASLC International Lymph Node Map and the accompanying table of anatomical boundaries is the recognized means of describing regional node involvement in lung cancer by the Union International for Cancer Control and American Joint Committee on Cancer.

Recommendations

Standardized reporting required for accurate TNM staging should include size, chest wall, and mediastinal contact. An interdisciplinary board should develop standardized reports for lung cancer staging and follow-up. Such reports are already in use in, for example, breast and prostate cancer imaging.

Radiology reports should describe all information that can help to improve accurate clinical TNM staging.

Lymph nodes should be described according to the IASLC lymph node map and table of definitions.

Volumetric Tumor Measurements/Novel Morphological Signs for Therapy Response

No agreement was achieved on how to standardize interpretation of tumor cavitation in patients that do not undergo dedicated targeted therapy. However, there was a consensus that cavitation should be considered as a sign of therapy response in patients that undergo targeted therapy, although there is no knowledge on how this finding can be integrated in ongoing studies that simply use RECIST criteria.

Volumetric measurement methods to follow-up indeterminate nodules and tumor therapy were discussed. There was a broad consensus that current data strongly support the use of volumetric tumor measurements and that these measurements are superior to uni- or bi-dimensional measurements.

Recommendations

Volumetric measurements should be included within future studies (prospectively collected data on volumetric tumor size). Follow-up of indeterminate solitary pulmonary nodules should be performed using volumetric measurements.

Prospective trials are needed to investigate the clinical value of tumor cavitation during therapy, to provide more evidence on this phenomenon, and to provide recommendations on how to integrate cavitation and decreasing tumor density into RECIST or WHO criteria.

Specific Issues–SUV Variance between Different Manufacturers

It was highlighted that measured SUV for PET imaging largely differ between manufacturers. This significantly limits the value of PET in multicenter/multivendor studies. It was also pointed out that there is no agreement which SUV should be measured or used in clinical studies (SUV_{max} versus SUV_{mean}). Therefore, the group concordantly emphasized the need for a higher level of standardization in clinical studies to generate manufacturer-independent thresholds for PET imaging. It was mentioned in the discussion that SUV could be systematically recorded to potentially include those values in upcoming TNM editions.

Recommendations

The industry should be encouraged intensify efforts to standardize SUV measurement between different PET systems. However, imaging centers are also in charge to work on higher standardized scanning and measurement techniques.

Specific Issues—Mesothelioma

For the accurate staging of mesothelioma, there is a lack of evidence for all imaging modalities. Moreover, assessment of therapy response is still insufficient and not globally standardized. There was a consensus that specific volumetric software applications are specifically useful for the challenging staging and response assessment in patients with mesothelioma.

Recommendations

^{18}F-FDG PET–CT and DECT combine metabolic information and high soft tissue resolution as well as information on total tumor blood volume that can be used for volumetric measurement. Further research on these modalities is therefore required.

Specific Issues—Thymic Tumors

The correct staging of thymic tumors is an unsolved problem. Because the tumor is localized in the mediastinum, 18F-PET–MRI would be an interesting tool. However, thymic tumors are rare, and ^{18}F-PET–MRI is expensive and not broadly available. DW-MRI, on the other hand, is broadly available and has no additional cost.

Recommendations

In thymic tumors, DW-MRI should be evaluated as add on to standard imaging techniques to acquire additional data to better establish the value of the technique and to create stronger evidence for this rare tumor entity. Moreover, due to the worldwide relative small number of thymic tumors the set-up of a dedicated imaging database that includes DW-MRI should be discussed.

CONCLUSION

In summary, the discussion during this first interdisciplinary imaging advisory board came to the conclusion that a more intense and regular communication among radiologists, nuclear medicine specialists, pneumologists, thoracic oncologists, preclinical researchers, radiation oncologists, and thoracic surgeons on novel imaging techniques and their potential value for thoracic oncology is highly required. Moreover, although several of the described functional imaging techniques are not yet "*ready for prime time*" to replace traditional imaging techniques, a more frequent integration of the techniques into prospective clinical trials could help to generate stronger evidence about the right use of these promising techniques. This allows advanced functional and molecular imaging being part of precision medicine in thoracic oncology.

REFERENCES

1. Rami-Porta R, Crowley JJ, Goldstraw P. The revised TNM staging system for lung cancer. *Ann Thorac Cardiovasc Surg* 2009;15:4–9.
2. Rengan R, Maity AM, Stevenson JP, Hahn SM. New strategies in non-small cell lung cancer: improving outcomes in chemoradiotherapy for locally advanced disease. *Clin Cancer Res* 2011;17:4192–4199.
3. Miles K. Can imaging help improve the survival of cancer patients? *Cancer Imaging* 2011;11:S86–S92.
4. Nishino M, Jackman DM, Hatabu H, Jänne PA, Johnson BE, Van den Abbeele AD. Imaging of lung cancer in the era of molecular medicine. *Acad Radiol* 2011;18:424–436.
5. Nishino M, Jagannathan JP, Ramaiya NH, Van den Abbeele AD. Revised RECIST guideline version 1.1: What oncologists want to know and what radiologists need to know. *AJR Am J Roentgenol* 2010;195:281–289.
6. Nishino M, Jagannathan JP, Krajewski KM, et al. Personalized tumor response assessment in the era of molecular medicine: Cancer-specific and therapy-specific response criteria to complement pitfalls of RECIST. *AJR Am J Roentgenol* 2012;198:737–745.
7. Oxnard GR, Morris MJ, Hodi FS, et al. When progressive disease does not mean treatment failure: Reconsidering the criteria for progression. *J Natl Cancer Inst* 2012;104:1534–1541.
8. Stacchiotti S, Collini P, Messina A, et al. High-grade soft-tissue sarcomas: Tumor response assessment–pilot study to assess the correlation between radiologic and pathologic response by using RECIST and Choi criteria. *Radiology* 2009;251:447–456.
9. Zhao B, Tan Y, Bell DJ, et al. Exploring intra- and inter-reader variability in uni-dimensional, bi-dimensional, and volumetric measurements of solid tumors on CT scans reconstructed at different slice intervals. *Eur J Radiol* 2013;82:959–968.
10. Marten K, Auer F, Schmidt S, Kohl G, Rummeny EJ, Engelke C. Inadequacy of manual measurements compared to automated CT volumetry in assessment of treatment response of pulmonary metastases using RECIST criteria. *Eur Radiol* 2006;16:781–790.
11. Zhao B, Schwartz LH, Moskowitz CS, Ginsberg MS, Rizvi NA, Kris MG. Lung cancer: Computerized quantification of tumor response–initial results. *Radiology* 2006;241:892–898.
12. Zhao B, James LP, Moskowitz CS, et al. Evaluating variability in tumor measurements from same-day repeat CT scans of patients with non-small cell lung cancer. *Radiology* 2009;252:263–272.
13. Mozley PD, Schwartz LH, Bendtsen C, Zhao B, Petrick N, Buckler AJ. Change in lung tumor volume as a biomarker of treatment response: a critical review of the evidence. *Ann Oncol* 2010;21:1751–1755.
14. Mozley PD, Bendtsen C, Zhao B, et al. Measurement of tumor volumes improves RECIST-based response assessments in advanced lung cancer. *Transl Oncol* 2012;5:19–25.

15. Nishino M, Guo M, Jackman DM, et al. CT tumor volume measurement in advanced non-small-cell lung cancer: Performance characteristics of an emerging clinical tool. *Acad Radiol* 2011;18:54–62.
16. Dehing-Oberije C, De Ruysscher D, van der Weide H, et al. Tumor volume combined with number of positive lymph node stations is a more important prognostic factor than TNM stage for survival of non-small-cell lung cancer patients treated with (chemo)radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;70:1039–1044.
17. Alexander BM, Othus M, Caglar HB, Allen AM. Tumor volume is a prognostic factor in non-small-cell lung cancer treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2011;79:1381–1387.
18. Kozak MM, Murphy JD, Schipper ML, et al. Tumor volume as a potential imaging-based risk-stratification factor in trimodality therapy for locally advanced non-small cell lung cancer. *J Thorac Oncol* 2011;6:920–926.
19. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. *Clin Cancer Res* 2009;15:7412–7420.
20. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: Proposal of new computed tomography response criteria. *J Clin Oncol* 2007;25:1753–1759.
21. Riely GJ, Kris MG, Zhao B, et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. *Clin Cancer Res* 2007;13:5150–5155.
22. Jackman D, Pao W, Riely GJ, et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *J Clin Oncol* 2010;28:357–360.
23. Nishino M, Dahlberg SE, Cardarella S, et al. Tumor volume decrease at 8 weeks is associated with longer survival in EGFR-mutant advanced non-small-cell lung cancer patients treated with EGFR TKI. *J Thorac Oncol* 2013;8:1059–1068.
24. Lee HY, Lee KS, Ahn MJ, et al. New CT response criteria in non-small cell lung cancer: Proposal and application in EGFR tyrosine kinase inhibitor therapy. *Lung Cancer* 2011;73:63–69.
25. Chaft JE, Rusch V, Ginsberg MS, et al. Phase II trial of neoadjuvant bevacizumab plus chemotherapy and adjuvant bevacizumab in patients with resectable nonsquamous non-small-cell lung cancers. *J Thorac Oncol* 2013;8:1084–1090.
26. Johnson TR, Krauss B, Sedlmair M, et al. Material differentiation by dual energy CT: Initial experience. *Eur Radiol* 2007;17:1510–1517.
27. Henzler T, Fink C, Schoenberg SO, Schoepf UJ. Dual-energy CT: Radiation dose aspects. *AJR Am J Roentgenol* 2012;199:S16–S25.
28. Chae EJ, Song JW, Seo JB, Krauss B, Jang YM, Song KS. Clinical utility of dual-energy CT in the evaluation of solitary pulmonary nodules: Initial experience. *Radiology* 2008;249:671–681.
29. Apfaltrer P, Meyer M, Meier C, et al. Contrast-enhanced dual-energy CT of gastrointestinal stromal tumors: Is iodine-related attenuation a potential indicator of tumor response? *Invest Radiol* 2012;47:65–70.
30. Je Y, Schutz FA, Choueiri TK. Risk of bleeding with vascular endothelial growth factor receptor tyrosine-kinase inhibitors sunitinib and sorafenib: A systematic review and meta-analysis of clinical trials. *Lancet Oncol* 2009;10:967–974.
31. Altenbernd J, Heusner TA, Ringelstein A, Ladd SC, Forsting M, Antoch G. Dual-energy-CT of hypervascular liver lesions in patients with HCC: Investigation of image quality and sensitivity. *Eur Radiol* 2011;21:738–743.
32. Graser A, Becker CR, Staehler M, et al. Single-phase dual-energy CT allows for characterization of renal masses as benign or malignant. *Invest Radiol* 2010;45:399–405.
33. Schmid-Bindert G, Henzler T, Chu TQ, et al. Functional imaging of lung cancer using dual energy CT: How does iodine related attenuation correlate with standardized uptake value of 18FDG-PET-CT? *Eur Radiol* 2012;22:93–103.
34. Kim YN, Lee HY, Lee KS, et al. Dual-energy CT in patients treated with anti-angiogenic agents for non-small cell lung cancer: New method of monitoring tumor response? *Korean J Radiol* 2012;13:702–710.
35. Ogawa M, Hara M, Imafuji A, et al. Dual-energy CT can evaluate both hilar and mediastinal lymph nodes and lesion vascularity with a single scan at 60 seconds after contrast medium injection. *Acad Radiol* 2012;19:1003–1010.
36. Yanagita H, Honda N, Nakayama M, et al. Prediction of postoperative pulmonary function: Preliminary comparison of single-breath dual-energy xenon CT with three conventional methods. *Jpn J Radiol* 2013;31:377–385.
37. Li Y, Yang ZG, Chen TW, Deng YP, Yu JQ, Li ZL. Whole tumour perfusion of peripheral lung carcinoma: Evaluation with first-pass CT perfusion imaging at 64-detector row CT. *Clin Radiol* 2008;63:629–635.
38. Swensen SJ. Functional CT: Lung nodule evaluation. *Radiographics* 2000;20:1178–1181.
39. Swensen SJ, Brown LR, Colby TV, Weaver AL. Pulmonary nodules: CT evaluation of enhancement with iodinated contrast material. *Radiology* 1995;194:393–398.
40. Swensen SJ, Morin RL, Schueler BA, et al. Solitary pulmonary nodule: CT evaluation of enhancement with iodinated contrast material–a preliminary report. *Radiology* 1992;182:343–347.
41. Swensen SJ, Viggiano RW, Midthun DE, et al. Lung nodule enhancement at CT: Multicenter study. *Radiology* 2000;214:73–80.
42. Yamashita K, Matsunobe S, Tsuda T, et al. Solitary pulmonary nodule: Preliminary study of evaluation with incremental dynamic CT. *Radiology* 1995;194:399–405.
43. Zhang M, Kono M. Solitary pulmonary nodules: Evaluation of blood flow patterns with dynamic CT. *Radiology* 1997;205:471–478.
44. Tateishi U, Kusumoto M, Nishihara H, Nagashima K, Morikawa T, Moriyama N. Contrast-enhanced dynamic computed tomography for the evaluation of tumor angiogenesis in patients with lung carcinoma. *Cancer* 2002;95:835–842.
45. Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. *Science* 2003;300:1155–1159.
46. Ng QS, Goh V, Milner J, Padhani AR, Saunders MI, Hoskin PJ. Acute tumor vascular effects following fractionated radiotherapy in human lung cancer: In vivo whole tumor assessment using volumetric perfusion computed tomography. *Int J Radiat Oncol Biol Phys* 2007;67:417–424.
47. Wang J, Wu N, Cham MD, Song Y. Tumor response in patients with advanced non-small cell lung cancer: Perfusion CT evaluation of chemotherapy and radiation therapy. *AJR Am J Roentgenol* 2009;193:1090–1096.
48. Lind JS, Meijerink MR, Dingemans AM, et al. Dynamic contrast-enhanced CT in patients treated with sorafenib and erlotinib for non-small cell lung cancer: A new method of monitoring treatment? *Eur Radiol* 2010;20:2890–2898.
49. Fraioli F, Anzidei M, Zaccagna F, et al. Whole-tumor perfusion CT in patients with advanced lung adenocarcinoma treated with conventional and antiangiogenetic chemotherapy: Initial experience. *Radiology* 2011;259:574–582.
50. Sauter AW, Merkle A, Schulze M, et al. Intraobserver and interobserver agreement of volume perfusion CT (VPCT) measurements in patients with lung lesions. *Eur J Radiol* 2012;81:2853–2859.
51. Shi J, Schmid-Bindert G, Fink C, et al. Dynamic volume perfusion CT in patients with lung cancer: Baseline perfusion characteristics of different histological subtypes. *Eur J Radiol* 2013;82:e894–e900.
52. Peters S, Adjei AA, Gridelli C, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23:vii56–vii64.
53. De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2014;45:787–798.
54. Crinò L, Weder W, van Meerbeeck J, Felip E; ESMO Guidelines Working Group. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:v103–v115.
55. Toba H, Sakiyama S, Otsuka H, et al. 18F-fluorodeoxyglucose positron emission tomography/computed tomography is useful in postoperative follow-up of asymptomatic non-small-cell lung cancer patients. *Interact Cardiovasc Thorac Surg* 2012;15:859–864.
56. Takenaka D, Ohno Y, Koyama H, et al. Integrated FDG-PET/CT vs. standard radiological examinations: Comparison of capability for assessment of postoperative recurrence in non-small cell lung cancer patients. *Eur J Radiol* 2010;74:458–464.

57. Rubins J, Unger M, Colice GL; American College of Chest Physicians. Follow-up and surveillance of the lung cancer patient following curative intent therapy: ACCP evidence-based clinical practice guideline (2nd edition). *Chest* 2007;132:355S–367S.
58. Keidar Z, Haim N, Guralnik L, et al. PET/CT using 18F-FDG in suspected lung cancer recurrence: Diagnostic value and impact on patient management. *J Nucl Med* 2004;45:1640–1646.
59. Kanzaki R, Higashiyama M, Maeda J, et al. Clinical value of F18-fluorodeoxyglucose positron emission tomography-computed tomography in patients with non-small cell lung cancer after potentially curative surgery: Experience with 241 patients. *Interact Cardiovasc Thorac Surg* 2010;10:1009–1014.
60. Jiménez-Bonilla JF, Quirce R, Martínez-Rodríguez I, et al. Diagnosis of recurrence and assessment of post-recurrence survival in patients with extracranial non-small cell lung cancer evaluated by 18F-FDG PET/CT. *Lung Cancer* 2013;81:71–76.
61. Inoue T, Kim EE, Komaki R, et al. Detecting recurrent or residual lung cancer with FDG-PET. *J Nucl Med* 1995;36:788–793.
62. Cuaron J, Dunphy M, Rimner A. Role of FDG-PET scans in staging, response assessment, and follow-up care for non-small cell lung cancer. *Front Oncol* 2012;2:208.
63. Choi SH, Kim YT, Kim SK, et al. Positron emission tomography-computed tomography for postoperative surveillance in non-small cell lung cancer. *Ann Thorac Surg* 2011;92:1826–32;discussion 1832.
64. Caulo A, Mirsadraee S, Maggi F, Leccisotti L, van Beek EJ, Bonomo L. Integrated imaging of non-small cell lung cancer recurrence: CT and PET-CT findings, possible pitfalls and risk of recurrence criteria. *Eur Radiol* 2012;22:588–606.
65. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 2009;50:122S–150S.
66. Nestle U, Kremp S, Grosu AL. Practical integration of [18F]-FDG-PET and PET-CT in the planning of radiotherapy for non-small cell lung cancer (NSCLC): The technical basis, ICRU-target volumes, problems, perspectives. *Radiother Oncol* 2006;81:209–225.
67. Grills IS, Yan D, Black QC, Wong CY, Martinez AA, Kestin LL. Clinical implications of defining the gross tumor volume with combination of CT and 18FDG-positron emission tomography in non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2007;67:709–719.
68. Deniaud-Alexandre E, Touboul E, Lerouge D, et al. Impact of computed tomography and 18F-deoxyglucose coincidence detection emission tomography image fusion for optimization of conformal radiotherapy in non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2005;63:1432–1441.
69. Teng FF, Meng X, Sun XD, Yu JM. New strategy for monitoring targeted therapy: Molecular imaging. *Int J Nanomedicine* 2013;8: 3703–3713.
70. Zander T, Scheffler M, Nogova L, et al. Early prediction of nonprogression in advanced non-small-cell lung cancer treated with erlotinib by using [(18)F]fluorodeoxyglucose and [(18)F]fluorothymidine positron emission tomography. *J Clin Oncol* 2011;29:1701–1708.
71. Kahraman D, Scheffler M, Zander T, et al. Quantitative analysis of response to treatment with erlotinib in advanced non-small cell lung cancer using 18F-FDG and 3'-deoxy-3'-18F-fluorothymidine PET. *J Nucl Med* 2011;52:1871–1877.
72. Ullrich RT, Zander T, Neumaier B, et al. Early detection of erlotinib treatment response in NSCLC by 3'-deoxy-3'-[F]-fluoro-L-thymidine ([F]FLT) positron emission tomography (PET). *PLoS One* 2008;3:e3908.
73. Kayani I, Conry BG, Groves AM, et al. A comparison of 68Ga-DOTATATE and 18F-FDG PET/CT in pulmonary neuroendocrine tumors. *J Nucl Med* 2009;50:1927–1932.
74. D'Addario G, Früh M, Reck M, Baumann P, Klepetko W, Felip E; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:v116–v119.
75. Takenaka D, Ohno Y, Matsumoto K, et al. Detection of bone metastases in non-small cell lung cancer patients: Comparison of whole-body diffusion-weighted imaging (DWI), whole-body MR imaging without and with DWI, whole-body FDG-PET/CT, and bone scintigraphy. *J Magn Reson Imaging* 2009;30:298–308.
76. Qu X, Huang X, Yan W, et al. A meta-analysis of (1)(8)FDG-PET-CT, (1)(8)FDG-PET, MRI and bone scintigraphy for diagnosis of bone metastases in patients with lung cancer. *Eur J Radiol* 2012;81:1007–1015.
77. Chang MC, Chen JH, Liang JA, et al. Meta-analysis: Comparison of F-18 fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastasis in patients with lung cancer. *Acad Radiol* 2012;19:349–357.
78. Koşucu P, Tekinbaş C, Erol M, et al. Mediastinal lymph nodes: Assessment with diffusion-weighted MR imaging. *J Magn Reson Imaging* 2009;30:292–297.
79. Wu LM, Xu JR, Gu HY, et al. Preoperative mediastinal and hilar nodal staging with diffusion-weighted magnetic resonance imaging and fluorodeoxyglucose positron emission tomography/computed tomography in patients with non-small-cell lung cancer: Which is better? *J Surg Res* 2012;178:304–314.
80. Yeh DW, Lee KS, Han J, et al. Mediastinal nodes in patients with non-small cell lung cancer: MRI findings with PET/CT and pathologic correlation. *AJR Am J Roentgenol* 2009;193:813–821.
81. Sommer G, Wiese M, Winter L, et al. Preoperative staging of non-small-cell lung cancer: Comparison of whole-body diffusion-weighted magnetic resonance imaging and 18F-fluorodeoxyglucose-positron emission tomography/computed tomography. *Eur Radiol* 2012;22: 2859–2867.
82. Ohno Y, Koyama H, Yoshikawa T, et al. N stage disease in patients with non-small cell lung cancer: Efficacy of quantitative and qualitative assessment with STIR turbo spin-echo imaging, diffusion-weighted MR imaging, and fluorodeoxyglucose PET/CT. *Radiology* 2011;261:605–615.
83. Nakayama J, Miyasaka K, Omatsu T, et al. Metastases in mediastinal and hilar lymph nodes in patients with non-small cell lung cancer: Quantitative assessment with diffusion-weighted magnetic resonance imaging and apparent diffusion coefficient. *J Comput Assist Tomogr* 2010;34:1–8.
84. Hasegawa I, Boiselle PM, Kuwabara K, Sawafuji M, Sugiura H. Mediastinal lymph nodes in patients with non-small cell lung cancer: Preliminary experience with diffusion-weighted MR imaging. *J Thorac Imaging* 2008;23:157–161.
85. Nomori H, Mori T, Ikeda K, et al. Diffusion-weighted magnetic resonance imaging can be used in place of positron emission tomography for N staging of non-small cell lung cancer with fewer false-positive results. *J Thorac Cardiovasc Surg* 2008;135:816–822.
86. Ohno Y, Koyama H, Yoshikawa T, et al. Diffusion-weighted MRI versus 18F-FDG PET/CT: Performance as predictors of tumor treatment response and patient survival in patients with non-small cell lung cancer receiving chemoradiotherapy. *AJR Am J Roentgenol* 2012;198:75–82.
87. Reshkin SJ, Bellizzi A, Caldeira S, et al. Na+/H+ exchanger-dependent intracellular alkalinization is an early event in malignant transformation and plays an essential role in the development of subsequent transformation-associated phenotypes. *FASEB J* 2000;14:2185–2197.
88. Hilal SK, Maudsley AA, Ra JB, et al. In vivo NMR imaging of sodium-23 in the human head. *J Comput Assist Tomogr* 1985;9:1–7.
89. Konstandin S, Nagel AM, Heiler PM, Schad LR. Two-dimensional radial acquisition technique with density adaption in sodium MRI. *Magn Reson Med* 2011;65:1090–1096.
90. Haneder S, Konstandin S, Morelli JN, et al. Quantitative and qualitative (23)Na MR imaging of the human kidneys at 3 T: Before and after a water load. *Radiology* 2011;260:857–865.
91. Boada FE, Shen GX, Chang SY, Thulborn KR. Spectrally weighted twisted projection imaging: Reducing T2 signal attenuation effects in fast three-dimensional sodium imaging. *Magn Reson Med* 1997;38:1022–1028.
92. Bottomley PA, Lee RF, Constantinides CD, Ouwerkerk R, Weiss RG. Quantification and imaging of myocardial sodium and creatine kinase metabolites. *MAGMA* 2000;11:39–41.
93. Ouwerkerk R, Bleich KB, Gillen JS, Pomper MG, Bottomley PA. Tissue sodium concentration in human brain tumors as measured with 23Na MR imaging. *Radiology* 2003;227:529–537.
94. Ouwerkerk R, Jacobs MA, Macura KJ, et al. Elevated tissue sodium concentration in malignant breast lesions detected with non-invasive 23Na MRI. *Breast Cancer Res Treat* 2007;106:151–160.

95. Henzler T, Konstandin S, Schmid-Bindert G, et al. Imaging of tumor viability in lung cancer: Initial results using 23Na-MRI. *Rofo* 2012;184:340–344.
96. Heusch P, Buchbender C, Köhler J, et al. Thoracic staging in lung cancer: Prospective comparison of 18F-FDG PET/MR imaging and 18F-FDG PET/CT. *J Nucl Med* 2014;55:373–378.
97. Al-Nabhani KZ, Syed R, Michopoulou S, et al. Qualitative and quantitative comparison of PET/CT and PET/MR imaging in clinical practice. *J Nucl Med* 2014;55:88–94.
98. Kim YN, Yi CA, Lee KS, et al. A proposal for combined MRI and PET/CT interpretation criteria for preoperative nodal staging in non-small-cell lung cancer. *Eur Radiol* 2012;22:1537–1546.
99. Padhani AR, Fishman EK, Heitmiller RF, Wang KP, Wheeler JH, Kuhlman JE. Multiplanar display of spiral CT data of the pulmonary hila in patients with lung cancer. Preliminary observations. *Clin Imaging* 1995;19:252–257.
100. Stöblen F, Neumann K, Eberhardt W, et al. CT angiography of the pulmonary artery in patients with bronchial carcinoma. *Langenbecks Arch Chir Suppl Kongressbd* 1997;114:1277–1279.
101. Wang JW, Wu N, Zhu Q, Huang Y. Application of spiral CT and post-image processing technique in the staging of central lung cancer. *Zhonghua Zhong Liu Za Zhi* 2003;25:74–77.
102. Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P; Members of IASLC Staging Committee. The IASLC lung cancer staging project: A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;4:568–577.

